Therefore, the rejection under the Written Description Requirement with respect to transgenics is inapplicable and should be withdrawn.

Claims 1 and 23 have been amended to include the feature that the cells contain a dominant negative form of a PMS2 gene. Without conceding the correctness of the Examiner's argument with respect to fulfillment of the Written Description Requirement as to other forms of mismatch repair genes, Applicants hereby amend the claims to recite that the mismatch repair gene is a PMS2 dominant negative. Applicants hereby also reserve the right to pursue claims directed to other mismatch repair genes in one or more divisional applications.

The claims, as amended are drawn to cells comprising a dominant negative form of a PMS2 gene and methods of making hypermutable antibody-producing cells using a dominant negative form of a PMS2 gene. The Specification as filed clearly describes the PMS2 gene and a specific dominant negative form of the PMS2 gene: a truncation mutant. The Specification describes at page 10, lines 18-30 through page 11, lines 1-7 that dominant negative alleles may be selected from organisms and screened for dominant negative effect on the cells. The specification provides methods for analyzing the dominant negative mutations and protocols for screening the candidate dominant negative mutations. Furthermore, the Specification provides nucleotide and amino acid sequences for both human and mouse PMS2 as examples of PMS2 genes which are deemed PMS2 genes and proteins due to their high homology. One of skill in the art can easily identify other PMS2 genes through homology (as is the standard in the art) and perform manipulations and screening of these genes to identify dominant negative

mutants of PMS2. Clearly, the Applicants were in possession of the embodiments of the invention comprising dominant negative mutants of PMS2.

Applicants earnestly submit that the Written Description Requirement is fulfilled with respect to the amended claims.

2. Enablement

The Office Action also rejects claims 1-4, 9-11, 22-25, and 29 under 35 U.S.C. §112, first paragraph, as enabling only for cells comprising the dominant negative allele *hPMS2-134*, and a culture of cells wherein the cells comprise the dominant negative allele *hPMS2-134*. The Office Action alleges that the claims are not commensurate with the scope of the disclosure, such that undue experimentation would be necessary to make and use the invention. Applicants respectfully disagree, however, without conceding the correctness of the Examiner's argument regarding the use of other dominant mismatch repair genes, Claims 1 and 23 have been amended to include the feature that the dominant negative gene is a PMS2 gene. As stated above, Applicants reserve the right to pursue claims directed to other mismatch repair genes in one or more divisional applications.

The amended claims are drawn to a cell or culture of cells that produce antibodies and the cells comprise a dominant negative allele of a PMS2 mismatch repair gene. In a working example, the dominant negative allele, PMS2-134 is used. The specification provides methods for analyzing the dominant negative mutations and protocols for screening the candidate dominant negative mutations. Furthermore, the Specification provides nucleotide and amino acid sequences for both human and mouse PMS2 as examples of PMS2 genes. One of skill in the art can easily identify other PMS2 genes

and perform manipulations and screening of these genes to identify dominant negative mutants of PMS2. Thus, the Specification provides the necessary guidance to determine dominant negative alleles for PMS2 mismatch repair genes and assays for function of such genes, such that one could practice the invention without undue experimentation. It must be remembered that even a significant amount of experimentation is permitted, so long as it is not undue. Of particular relevance is the fact that the specification provides guidance as to the genes that may be employed (*i.e.*, *PMS2*), and provides specific assays to identify alleles that exert the dominant negative effect when expressed. Thus, the Specification enables the use of dominant negative PMS2.

The Office Action also contains a lengthy section discussing how transgenic animals are not enabled by the Specification. This is apparently erroneously included in the Office Action as none of the claims under consideration is drawn to transgenic animals, but methods of making hypermutable antibody-producing cells and homogeneous cultures of cells. To the extent that the Examiner may have considered the claims as filed to cover introduction of the dominant negative allele into a fertilized egg to produce a transgenic animals which were "capable of producing antibodies," the claims, as amended are drawn to cells which do produce antibodies. Thus, the claims, as amended, do not read on transgenic animals, making this ground of rejection moot. Applicants respectfully request that the Examiner withdraw the rejection of the claims 35 U.S.C. §112, first paragraph with regard to the transgenic animal arguments.

The Office Action also contains a lengthy discussion of the claims as they relate to a method of gene therapy. Applicants do not fully understand the basis of the rejection as the claims do not describe a method of gene therapy. Rather the claims under

consideration relate to cells that produce antibodies being rendered hypermutable, such that the antibodies so produced will acquire mutations and phenotypes. The claims are not drawn to gene therapy which typically involves the introduction of a polynucleotide in order to have a therapeutic outcome on a particular disease state. As the claims as amended to do read on methods of gene therapy, Applicants respectfully request that the Examiner withdraw this basis of rejection under 35 U.S.C. §112, first paragraph.

Applicants earnestly submit that the amended claims are enabled by the specification.

35 U.S.C. §102(b), (e) and (f)

The Office Action rejects claims 1-4, 9-11, 22-25, and 29 under 35 U.S.C. §102(b) over Nicolaides *et al.* (1998) *Mol. Cell. Biol.* 18(3):1635-1641 ("Nicolaides"), or, in the alternative, under 35 U.S.C. §102(e) over U.S. Patent No. 6,146,894 to Nicolaides *et al.* ("the '894 patent"). The Office Action further rejects the claims under 35 U.S.C. §102(f) over the '894 patent.

The Office Action alleges that both Nicolaides and the '894 patent teach a method for transfecting a polynucleotide encoding hPMS2-134 into a cell which is capable of producing antibodies. The Office Action states that, absent evidence to the contrary, the cells disclosed in Nicolaides and/or the '894 patent are "capable of producing antibodies." The claims have been amended to recite that the cells receiving the dominant negative allele produce antibodies. That is, they are not merely capable of producing antibodies, but actually do produce antibodies. Neither the '894 patent nor Nicolaides specifically teach the introduction of dominant negative alleles of mismatch

repair genes into cells that produce antibodies, whether these cells are lymphoid cells or cells transfected with antibody genes. As the references do not teach all the limitations of the claims, as amended, the rejection under 35 U.S.C. §102(b), (e) and (f) should be withdrawn.

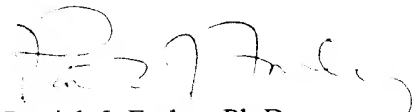
Obviousness-Type Double Patenting

As Applicants claims are distinct from those of the cited art, the double patenting is moot.

CONCLUSION

Applicants earnestly submit that the claims are in condition for allowance, which action is respectfully requested.

Respectfully submitted,



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Version with Markings to Show Changes Made

In the Claims

Please amend the claims as follows:

1. (Amended) A method for making a hypermutable, antibody-producing cell, comprising introducing into a cell [capable of producing] that produces [antibodies] a polynucleotide comprising a dominant negative allele of a PMS2 mismatch repair gene, wherein said antibody-producing cell becomes hypermutable.

22. (Amended) The method of claim 1 wherein [said capability is due to the co-introduction of] an immunoglobulin gene is co-introduced into said cell, whereby said cell produces said antibodies.

23. (Amended) A homogeneous culture of hypermutable, mammalian cells wherein said cells produces antibodies and comprise a dominant negative allele of a PMS2 mismatch repair gene.

25. (Amended) The culture of hypermutable, mammalian cells of claim [24] 23 wherein the mismatch repair gene is human *PMS2*.

Please cancel claims 3 and 24 without prejudice and without disclaimer as to the subject matter thereof.

Please enter the following new claims:

73. (New) A cell produced by the method of claim 1.

74. (New) A cell produced by the method of claim 4.

75. (New) The method of claim 1 further comprising the step restoring genetic stability of said hypermutable cell.

76. (New) A cell produced by the method of claim 75.

77. (New) A homogeneous culture of the cells of claim 76.

78. (New) The method of claim 22 further comprising the step restoring genetic stability of said hypermutable cell.

79. (New) A cell produced by the method of claim 78.

80. (New) A homogeneous culture of the cells of claim 79.

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No.	Doccode	Number of pages
1	LET.	4
2	A...	1
3	SPEC	1
4	REM	4
5	CRFL	2
6	SEQLIST	26

Total number of pages: 38

Remarks:

Order of re-scan issued on .....